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ORIGINAL WORK

Intracerebral Hemorrhage and Coronavirus Disease 2019 in a Cohort of 282,718 Hospitalized Patients

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Abstract

Background: To identify whether the risk of intracerebral hemorrhage is higher in patients with coronavirus disease 2019 (COVID-19), we compared the risk factors, comorbidities, and outcomes in patients intracerebral hemorrhage and COVID-19 and those without COVID-19.

Methods: We analyzed the data from the Cerner deidentified COVID-19 data set derived from 62 health care facilities. The data set included patients with an emergency department or inpatient encounter with discharge diagnoses codes that could be associated with suspicion of or exposure to COVID-19 or confirmed COVID-19.

Results: There were a total of 154 (0.2%) and 667 (0.3%) patients with intracerebral hemorrhage among 85,645 patients with COVID-19 and 197,073 patients without COVID-19, respectively. In the multivariate model, there was a lower risk of intracerebral hemorrhage in patients with COVID-19 (odds ratio 0.5; 95% confidence interval 0.5–0.6; $p < .0001$) after adjustment for sex, age strata, race/ethnicity, hypertension, diabetes mellitus, nicotine dependence/tobacco use, hyperlipidemia, atrial fibrillation, congestive heart failure, long-term anticoagulant use, and alcohol abuse. The proportions of patients who developed pneumonia (58.4% versus 22.5%; $p < .0001$), acute kidney injury (48.7% versus 31.0%; $p < .0001$), acute myocardial infarction (11% versus 6.4%; $p = .048$), sepsis (41.6% versus 22.5%; $p < .0001$), and respiratory failure (61.7% versus 42.3%; $p < .0001$) were significantly higher among patients with intracerebral hemorrhage and COVID-19 compared with those without COVID-19. The in-hospital mortality among patients with intracerebral hemorrhage and COVID-19 was significantly higher compared with that among those without COVID-19 (40.3% versus 19.0%; $p < .0001$).

Conclusions: Our analysis does not suggest that rates of intracerebral hemorrhage are higher in patients with COVID-19. The higher mortality in patients with intracerebral hemorrhage and COVID-19 compared with those without COVID-19 is likely mediated by higher frequency of comorbidities and adverse in-hospital events.

Keywords: COVID-19, Intracerebral hemorrhage, Death, Disability, Electronic medical records, SARS-CoV-2

Introduction

Cerebrovascular events are being increasingly recognized in patients with coronavirus disease 2019 (COVID-19) [1–3]. Anecdotal reports and small series have identified the occurrence of intracerebral hemorrhage in patients with COVID-19 [4–7]. The incidence of intracerebral hemorrhage ranged between 0.3 and 1.2% in a review of

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nine cohort studies ($n = 13{,}741$ patients with COVID-19). Although previous studies have evaluated the risk of ischemic stroke [8, 9], no study has evaluated the risk of intracerebral hemorrhage in patients with COVID-19. The CHEST Guideline and Expert Panel Report highlighted the need to quantify the risk of intracerebral hemorrhage in patients with COVID-19 because of increasing requirement of anticoagulation [10]. One of the challenges in evaluating a possible association is the low incidence of intracerebral hemorrhage, thus requiring a large cohort of patients with COVID-19 for adequate analysis. We performed this study to identify risk factors, comorbidities, treatment strategies, and outcomes in patients with intracerebral hemorrhage derived from a large cohort of patients with COVID-19.

Methods

We analyzed the data from the Cerner deidentified COVID-19 data set, a subset of Cerner Real-World Data [11–13]. The methodological aspects of the data set have been previously reported [13, 14]. We used the Cerner Real-World Data-COVID-2020Q3 version, which is based on electronic medical encounters between December 1, 2019, and November 13, 2020, from 62 acute care hospitals in the United States that have a data use agreement with Cerner Corporation.

The COVID-19 deidentified data set includes data for patients who qualified for inclusion on the basis of the following criteria:

1. Patient has a minimum of one emergency department or inpatient encounter with a diagnosis code (detailed list of 86 codes provided in previous publication [14] and in Supplemental Table 1) that could be associated with COVID-19 exposure or infection
2. Patient has a minimum of one emergency department or inpatient encounter with a positive laboratory test result for COVID-19

The data set includes both patients in whom COVID-19 was confirmed and those in whom the diagnosis was excluded, thereby, providing a control group for comparative analysis.

Patients with a positive laboratory test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were identified on the basis of Logical Observation Identifiers, Names, and Codes 41458-1, 94309-2, 94500-6, 94533-7, 94534-5, and 94646-7. These codes denote detection of SARS-CoV-2 RNA in respiratory (nasopharyngeal swabs, bronchoalveolar lavage, sputum) and other specimens or detection of the SARS-CoV-2N gene or *RdRp* gene in respiratory secretions by nucleic acid amplification with probe detection. Our analysis included only patients with prior medical history to ensure completeness of the records of potential comorbidities. Patients with prior medical history constituted approximately 76% of the total cohort of 490,373 patients.

Patients admitted with intracerebral hemorrhage were identified by *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) primary diagnosis code I61. We did not use ICD-10 code I62.9, which includes hemorrhagic transformation of ischemic stroke, in our analysis. There were 264 patients in our data set with ICD-10 code 162.9; however, all patients had a concurrent diagnosis of ischemic stroke. Other cardiovascular diseases were identified by using the *ICD-10-CM* codes as follows: hypertension (I10, O10.0, O10.9, I16, and I67.4), diabetes mellitus (E08), nicotine dependence (F17), alcohol use/abuse (F10), hyperlipidemia (E78), atrial fibrillation (I48), long-term anticoagulant use (Z79.01), and congestive heart failure (I09.81, I11.0, and I50).

The *ICD-10-CM* secondary diagnosis codes were used to identify those with new in-hospital events during acute hospitalization, such as ischemic stroke (including cerebral ischemia) (I63, I65, I66, I67.81, I67.82, and I67.89), cerebral edema (G93.5 and G93.6), acute kidney injury (N17), hepatic failure (K72), cardiac arrest (I46), respiratory failure (J96), pneumonia (J12–J18), urinary tract infection (N30.0, N30.9, N34.1, N34.2, and N39.0), transient cerebral ischemic attacks (G45), sepsis (including septic shock) (A41 and R65.21), deep venous thrombosis (I82), pulmonary embolism (I26), subarachnoid hemorrhage (I60), and acute myocardial infarction (I21). The procedures were identified by the *ICD-10 Procedure Coding System* as follows: intubation and mechanical ventilation (0BH17EZ and Z9911 or current procedural terminology codes 31500, 94656, and 94657 for intubation or 94002–94005 for mechanical ventilation), surgical evaluation (current procedural terminology codes 61313 and 61315), ventriculostomy (009600Z, 00960ZX, 00960ZZ, 009630Z, 00963ZX, 00963ZZ, 009640Z, 00964ZX, and 00964ZZ), intraventricular catheter placement (009630Z), intracranial pressure monitoring (4A003BD, 4A007BD, 4A008BD, 4A103BD, 4A107BD, and 4A108BD), and tracheostomy (0B113F4 and 0B110F4).

The outcome was based on discharge destination and categorized as home or nonroutine discharge (discharge to short-term hospital or other facility, including intermediate care and skilled nursing home), as previously used [13]. Previous studies [15, 16] have validated the use of discharge to home as a reliable surrogate for no disability to mild disability and nonroutine discharge, excluding death, for moderate to severe disability at 3 months post stroke [15, 16].

We performed this analysis to identify any significant differences in demographic and clinical characteristics, in-hospital events, and outcomes between patients with intracerebral hemorrhage with and without COVID-19, as well as patients with COVID-19 with and without intracerebral hemorrhage. We compared patients' age, sex, race/ethnicity, cardiovascular risk factors, length of stay, medical complications, procedures performed, and discharge status (categorized as nonroutine discharge or in-hospital death) for patients with intracerebral hemorrhage in strata based on presence or absence of COVID-19. We also analyzed the data from patients with COVID-19 to identify differences in the above-mentioned variables between patients with and without intracerebral hemorrhage. We used the χ^2 test for categorical data and the two-sample *t* test for continuous data to detect any significant differences in variables between the above-mentioned groups. Any *p* values less than 0.05 were considered significant.

We performed logistic regression analysis including all patients in the data set (patients with and without COVID-19) to identify the association between COVID-19 and intracerebral hemorrhage. We adjusted for known risk factors for intracerebral hemorrhage, including age (age strata < 35, 35–54, 55–70, and > 70 years), sex, race/ethnicity, hypertension, diabetes mellitus, nicotine dependence/tobacco use, hyperlipidemia, atrial fibrillation and congestive heart failure, long-term anticoagulant use, and alcohol use/abuse. All the analyses were done by using R (version 3.6.1).

Results

A total of 154 (0.2%) patients developed intracerebral hemorrhage among 85,645 patients with COVID-19, and 667 (0.3%) patients developed intracerebral hemorrhage among 197,073 patents without COVID-19.

Comparison Between Patients with Intracerebral Hemorrhage with and Without COVID-19

The mean age (± SD) of patients with intracerebral hemorrhage and COVID-19 was similar compared with that of those without COVID-19 (62.1 ± 17.2 versus 65.0 ± 17.6; $p = 0.0646$). The proportions of women (33.1% versus 45.3%; $p = 0.006$), and White patients (25.3% versus 54.3%; $p < 0.0001$) were lower, and the proportions of African American (20.8% versus 13.2%; $p = 0.0163$) and Hispanic patients (34.4% versus 21.6%; $p = 0.0008$) were higher among patients with intracerebral hemorrhage and COVID-19 compared with those without COVID-19 (see Table 1). The proportion of patients with alcohol use/abuse was lower (8.4% versus 14.7%; $p = 0.0409$) among patients with intracerebral hemorrhage and COVID-19 compared with those without COVID-19. There was no difference in the proportion of patients on long-term anticoagulation between patients with intracerebral hemorrhage with and without COVID-19 (27.9% versus 24.3%), but the proportion was significantly higher compared with patients with COVID-19 without intracerebral hemorrhage (27.9% versus 9.8%).

The proportions of patients who developed pneumonia, acute kidney injury, acute myocardial infarction, sepsis (including septic shock), and respiratory failure were significantly higher among patients with intracerebral hemorrhage and COVID-19 compared with those without COVID-19. The in-hospital mortality among patients with intracerebral hemorrhage and COVID-19 was significantly higher compared with those without COVID-19 (40.3% versus 19%; $p < 0.0001$). The rate of nonroutine discharge or in-hospital death was not different between patients with intracerebral hemorrhage and COVID-19 compared with those without COVID-19 (83.8% versus 78.3%; $p = 0.13$) (see Table 1).

Results of Multivariate Analysis

In the multivariate model, there was a lower risk of intracerebral hemorrhage in patients with COVID-19 (odds ratio [OR] 0.5; 95% confidence interval [CI] 0.5–0.6; $p < 0.0001$) after adjustment for sex, age strata, race/ethnicity, hypertension, diabetes mellitus, nicotine dependence/tobacco use, hyperlipidemia, atrial fibrillation, long-term anticoagulant use, alcohol use/abuse and congestive heart failure. Other risk factors independently associated with intracerebral hemorrhage were men (OR 1.4; 95% CI 1.2–1.7; $p < 0.0001$), age 35–54 years (OR 1.9; 95% CI 1.4–2.7; $p < 0.0001$), age 55–70 years (OR 2.9; 95% CI 2.1–4.0; $p < 0.0001$), age older than 70 years (OR 3.2; 95% CI 2.3–4.5; $p < 0.0001$), Hispanic ethnicity (OR 1.2; 95% CI 1.0–1.4; $p = 0.04$), hypertension (OR 3.0; 95% CI 2.4–3.7; $p < 0.0001$), alcohol use/abuse (OR 1.5; 95% CI 1.2–1.9; $p = 0.0002$), and atrial fibrillation (OR 1.9; 95% CI 1.6–2.3; $p < 0.0001$).

Comparison Between Patients with COVID-19 with and Without Intracerebral Hemorrhage

The mean age (± SD) of patients with COVID-19 and intracerebral hemorrhage was higher compared with that of those without intracerebral hemorrhage (62.1 ± 17.2 versus 49.7 ± 21.3; $p < 0.0001$) (see Table 1). The proportions of patients who had histories of hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, congestive heart failure, long-term anticoagulant use, or previous intracerebral hemorrhage were significantly higher among patients with COVID-19 and intracerebral hemorrhage. During the COVID-19 admissions, ischemic stroke, subarachnoid hemorrhage, transient cerebral

Table 1 Demographic and clinical characteristics and outcome of patients according to COVID-19 status and occurrence of intracerebral hemorrhage

Items	Patients with intracerebral hemorrhage and COVID-19 ($n=154$)	Patients with intracerebral hemorrhage but without COVID-19 ($n=667$)	p value[a]	Patients with COVID-19 but without intracerebral hemorrhage ($n=85,491$)	p value[b]
Age					
Mean ± SD (year)	62.1 ± 17.2	65.0 ± 17.6	.0646	49.7 ± 21.3	< .0001
Age < 35	12 (7.8%)	46 (6.9%)	.6958	24,938 (29.2%)	< .0001
Age 35–54	28 (18.2%)	111 (16.6%)	.6460	23,177 (27.1%)	.0127
Age 55–70	65 (42.2%)	216 (32.4%)	.0206	20,387 (23.8%)	< .0001
Age > 70	49 (31.8%)	294 (44.1%)	.0054	16,989 (19.9%)	.0002
Sex					
Men	103 (66.9%)	365 (54.7%)	.0060	38,594 (45.1%)	< .0001
Women	51 (33.1%)	302 (45.3%)	.0060	46,521 (54.4%)	< .0001
Race					
White, non-Hispanic	39 (25.3%)	362 (54.3%)	< .0001	26,585 (31.1%)	.1221
African American	32 (20.8%)	88 (13.2%)	.0163	16,331 (19.1%)	.5970
Hispanic	53 (34.4%)	144 (21.6%)	.0008	33,751 (39.5%)	.1990
Others	30 (19.5%)	73 (10.9%)	.0039	8,824 (10.3%)	.0002
Hypertension	126 (81.8%)	562 (84.3%)	.4589	40,755 (47.7%)	< .0001
Diabetes mellitus	76 (49.4%)	284 (42.6%)	.1269	26,305 (30.8%)	< .0001
Nicotine dependence/tobacco use	32 (20.8%)	183 (27.4%)	.0903	13,481 (15.8%)	.0884
Alcohol use/abuse	13 (8.4%)	98 (14.7%)	.0409	4,397 (5.1%)	.0643
Hyperlipidemia	78 (50.6%)	395 (59.2%)	.0524	29,102 (34%)	< .0001
Atrial fibrillation	49 (31.8%)	214 (32.1%)	.9492	8,591 (10%)	< .0001
Congestive heart failure	38 (24.7%)	197 (29.5%)	.2291	10,685 (12.5%)	< .0001
Long-term anticoagulant use	43 (27.9%)	162 (24.3%)	.3476	8,368 (9.8%)	< .0001
Previous intracerebral hemorrhage	28 (18.2%)	111 (16.6%)	.6460	285 (0.3%)	< .0001
In-hospital events					
Hospitalization duration (mean ± SD)	19 ± 18	14 ± 16	.0007	10 ± 12	< .0001
Ischemic stroke (including cerebral ischemia)	55 (35.7%)	232 (34.8%)	.8270	1,286 (1.5%)	< .0001
Subarachnoid hemorrhage	18 (11.7%)	87 (13%)	.6499	54 (0.1%)	< .0001
Transient cerebral ischemic attacks	2 (1.3%)	4 (0.6%)	.3586	177 (0.2%)	.0030
Cerebral edema	55 (35.7%)	266 (39.9%)	.3396	147 (0.2%)	< .0001
Pneumonia	90 (58.4%)	150 (22.5%)	< .0001	31,987 (37.4%)	< .0001
Deep venous thrombosis	15 (9.7%)	42 (6.3%)	.1297	1,363 (1.6%)	< .0001
Pulmonary embolism	3 (1.9%)	13 (1.9%)	.9994	1,194 (1.4%)	.5603
Urinary tract infection	25(16.2%)	136 (20.4%)	.2417	6309 (7.4%)	< .0001
Acute kidney injury	75 (48.7%)	207 (31%)	< .0001	12,245 (14.3%)	< .0001
Hepatic failure	11 (7.1%)	30 (4.5%)	.1744	862 (1%)	< .0001
Cardiac arrest	8 (5.2%)	33 (4.9%)	.8990	1417 (1.7%)	.0006
Acute myocardial infarction	17 (11%)	43 (6.4%)	.0484	2045 (2.4%)	< .0001
Sepsis, including septic shock	64 (41.6%)	150 (22.5%)	< .0001	11,827 (13.8%)	< .0001
Respiratory failure	95 (61.7%)	282 (42.3%)	< .0001	21,507 (25.2%)	< .0001
Received intubation/ mechanical ventilation[a,b]	46 (29.9%)	138 (20.7%)	.0138	3690 (4.3%)	< .0001
Received ventriculostomy	6 (3.9%)	52 (7.8%)	.0887	11 (0%)	< .0001
Received intraventricular catheter	5 (3.2%)	42 (6.3%)	.1420	8 (0%)	< .0001

Table 1 (continued)

Items	Patients with intracerebral hemorrhage and COVID-19 ($n=154$)	Patients with intracerebral hemorrhage but without COVID-19 ($n=667$)	p value[a]	Patients with COVID-19 but without intracerebral hemorrhage ($n=85,491$)	p value[b]
Received intracranial pressure monitoring	1 (0.6%)	6 (0.9%)	.7608	1 (0%)	< .0001
Received tracheostomy	6 (3.9%)	44 (6.6%)	.2065	420 (0.5%)	< .0001
Outcome					
Nonroutine discharge or in-hospital death	129 (83.8%)	522 (78.3%)	.1286	22,048 (25.8%)	< .0001
In-hospital death	62 (40.3%)	127 (19%)	< .0001	5,799 (6.8%)	< .0001

COVID-19 coronavirus disease 2019, *SD* standard deviation

[a] Comparison between patients with intracerebral hemorrhage and COVID-19 and those without COVID-19

[b] Comparison between patients with COVID-19 with intracerebral hemorrhage and those without intracerebral hemorrhage

ischemic attacks, pneumonia, deep venous thrombosis, urinary tract infection, acute kidney injury, hepatic failure, cardiac arrest, acute myocardial infarction, sepsis (including septic shock), and respiratory failure were more frequent in patients with COVID-19 and intracerebral hemorrhage.

The in-hospital mortality among patients with COVID-19 and intracerebral hemorrhage was significantly higher compared with that among patients with COVID-19 without intracerebral hemorrhage (40.3% versus 6.8%; $p<0.0001$). There was a significantly higher rate of nonroutine discharge or in-hospital death among patients with COVID-19 and intracerebral hemorrhage compared with those without intracerebral hemorrhage (83.8% versus 25.8%; $p<0.0001$) (see Table 1).

Discussion

Incidence of Intracerebral Hemorrhage in Patients with COVID-19

In our study, intracerebral hemorrhage occurred in 154 (0.2%) patients among 85,645 patients with COVID-19. Kvernland et al. [7] reported that hemorrhagic stroke (both nontraumatic intracerebral hemorrhage and spontaneous nonaneurysmal subarachnoid hemorrhage) occurred in 19 (0.5%) patients among 4071 patients with COVID-19 admitted within a large hospital system in New York. Melmed et al. [4] reported that intracerebral hemorrhage occurred in 35 (0.01%) patients among 3824 patients with COVID-19 admitted within another large hospital system in New York. In another study from Russia, Pavlov et al. [17] reported that intracerebral hemorrhage occurred in 3 (0.25%) patients among 1,200 patients with COVID-19. The pooled incidence of intracerebral hemorrhage in patients with COVID-19 was 0.7% (95% CI 0.5–0.9) in a review of 23 studies [18]. In our study, intracerebral hemorrhage occurred in 667 (0.3%) patients among 197,073 patents without COVID-19, which was higher than the occurrence rate in patients with COVID-19, suggesting no increase in risk among patients with COVID-19.

Effect of COVID-19 on Outcomes for Patients with Intracerebral Hemorrhage

We observed a relatively high in-hospital mortality rate of 40.3% among patients with intracerebral hemorrhage and COVID-19, which was twofold greater than the mortality rate (19%) observed in patients without COVID-19. Kvernland et al. [7] reported an in-hospital mortality rate of 84.6% among patients with COVID-19 and hemorrhagic stroke. Melmed et al. [4] reported that 52% of patients either died or were transitioned to hospice care among patients with COVID-19 and intracerebral hemorrhage. The average mortality rate was 48.6% among 148 patients with COVID-19 and intracerebral hemorrhage in a systematic review of 23 studies [18]. Only a small proportion of patients were discharged home in our study, suggesting that disability rates were also high among survivors of COVID-19 and intracerebral hemorrhage. Part of this higher mortality may be attributed to high rates of pneumonia, acute kidney injury, acute myocardial infarction, sepsis (including septic shock), and respiratory failure seen in patients with COVID-19 and intracerebral hemorrhage.

Implications for Practice

The high rates of multiorgan dysfunction manifesting as pneumonia, acute kidney injury, acute myocardial infarction, sepsis, and respiratory failure in patients with COVID-19 and intracerebral hemorrhage has three implications: (1) the treatment of neurological aspects of intracerebral hemorrhage alone may not be enough to reduce death or disability; (2) therapeutic strategies [19, 20] may have to expanded to include more measures toward identifying and addressing multiorgan failure; and

(3) quantitating multiorgan dysfunction using scales such as the Sequential Organ Failure Assessment should be incorporated with scales such as the intracerebral hemorrhage score as part of clinical assessment [21]. We did not observe an increased risk of intracerebral hemorrhage among patients with COVID-19. The proportion with intracerebral hemorrhage presumably related to long-term anticoagulation was similar between patients with intracerebral hemorrhage with and without COVID-19 in our study. Previous studies have suggested that anticoagulation-related intracerebral hemorrhages are relatively common in patients with COVID-19 [4, 7]. The absence of any excess risk due to COVID-19 beyond what is expected with anticoagulation may be reassuring because of the necessity of anticoagulation in patients with COVID-19 for both prevention and treatment of venous thromboembolism [10, 22]. Approximately 40–69% of patients with COVID-19 develop venous thromboembolism and will require anticoagulation [23, 24].

Limitations

Certain aspects of the analysis may need to be considered prior to interpretation of results. The analysis depends on the accuracy of diagnosis and procedures listed in the data collection system. The sensitivity (100%), specificity (98%) [25], and positive predictive value (96%) [26, 27] of ICD-10 diagnosis code I61 for identifying intracerebral hemorrhage are high. We acknowledge that the ICD-10 code used may include microhemorrhages depending on the interpretation of coding personnel, although this is unlikely to be used as primary diagnosis. Because of inherent limitations of the Cerner deidentified COVID-19 data set, we could not analyze differences in severity of neurological deficits (Glasgow Coma Scale) or hematoma volume and presence or absence of intraventricular hemorrhage. Therefore, we cannot definitely identify the underlying reasons for observed differences in outcomes between patients with intracerebral hemorrhage and COVID-19 and those without COVID-19. The patients with intracerebral hemorrhage without COVID-19 in the data set were those who were screened for COVID-19 because of either history of exposure or respiratory symptoms and may have other respiratory tract infections or even undetected COVID-19 depending on the thoroughness of screening [28–30] and may not be completely reflective of patients with intracerebral hemorrhage in the general population [13]. We used the destination of discharge as a surrogate for discharge functional outcome, similar to previous studies using Nationwide Inpatient Sample data [15, 31]. The discharge destination home has a high negative predictive value for identifying patients with a modified Rankin score of 2–6 at 3 months [16]. However, there are limitations to using discharge destination as a surrogate for functional outcome. Certain patients who were discharged home under hospice care may have severe disability. Some patients who were discharged to intermediate care may have recovered enough to be categorized as having mild disability and residing at home by 3 months.

Conclusions

Intracerebral hemorrhage was infrequent, and the risk was not increased in patients with COVID-19. The risk of death was increased in patients with intracerebral hemorrhage and COVID-19 compared with patients with intracerebral hemorrhage without COVID-19, and the risk of nonroutine discharge or in-hospital death was increased compared with patients with COVID-19 but without intracerebral hemorrhage. Part of the increased risk was likely mediated through higher frequencies of systemic comorbidities in these patients.

Supplementary Information
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Author contributions
All authors are responsible for (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

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Conflicts of Interest
The authors declare that they have no conflicts of interest.

Ethical approval/informed consent
The study complied with ethics standards, and institutional approval was obtained.

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